EXHIBIT 1

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	MDL No. 2606
THIS DOCUMENT RELATES TO ALL CASES	HON. ROBERT B. KUGLER

RULE 26 EXPERT REPORT OF BENJAMIN LEBWOHL REGARDING GENERAL CAUSATION

I have reviewed the documents, materials and literature identified in this report and the Appendices, including the reliance list set forth at Appendix 1. Based upon the analysis of these documents and materials, as well as my knowledge, experience, and training, and knowledge of the applicable literature, set forth herein and in my Curriculum Vitae attached as Appendix 2, I have formed opinions with regard to the question of whether Olmesartan Medoxomil causes sprue-like enteropathy and related gastrointestinal effects in a subset of users of the medication (referred to as "olmesartan enteropathy" herein). In evaluating and answering this question, I apply accepted scientific methodology, relying on the peer reviewed medical literature, and the process whereby olmesartan enteropathy has been identified and diagnosed in patients. Each of the opinions set forth is held to a reasonable degree of medical certainty.

SUMMARY OF QUALIFICATIONS AND EXPERIENCE

I am a board certified adult gastroenterologist based at the Celiac Disease Center at Columbia University, a major referral center for patients with celiac disease and related disorders. My current academic appointment is Assistant Professor of Medicine and Epidemiology. I joined the faculty of the Center in 2010 after completing a residency in internal medicine at Columbia and a fellowship in digestive and liver diseases, also at Columbia. My course of training included three years of training in internal medicine followed by an extra (optional) year as a chief medical resident, which consisted of teaching, administration, and leadership in the department of medicine, followed by three years of gastroenterology fellowship, which consisted of training in the clinical care of individuals with digestive and liver disease. This included exposure to inpatient and outpatient conditions, history and physical examination skills, medical decision making, and the performance of gastrointestinal procedures including esophagogastroduodenoscopy and colonoscopy. In addition to my clinical and academic appointments and work, I am on the Editorial Boards of Clinical and Translational Gastroenterology and Digestive Diseases and Sciences, and I serve as a peer reviewer for multiple journals, including but not limited to the New England Journal of Medicine, JAMA, Gastroenterology, and Gut. I have significant research interests, and I have co-authored 88 original research publications in the peer reviewed literature, along with numerous other academic publications.

During my three-year fellowship at Columbia I concurrently obtained a master's degree in Patient Oriented Research from the Department of Biostatistics at the Mailman School of Public Health, also at Columbia. While I was a student at the Mailman School I completed coursework in epidemiology and established research collaborations with investigators in the

Department of Epidemiology that continued after I completed my training. In 2011 I joined the faculty of the Department of Epidemiology at the school. My activities in the Department of Epidemiology have included advising master's students, serving as a research mentor for epidemiological research projects, lecturing to epidemiology students, and participating in the composition and grading of the written examination for PhD candidates in epidemiology. Although my primary area of training is in clinical gastroenterology, I have been invited to adjudicate in the dissertations by epidemiology PhD candidates both within my institution (Columbia) and outside institutions (University of Umea, Sweden and University of Calgary). I am being compensated for my time at a rate of $550/hour or $5000/full day in court or in a deposition. I have not previously testified in court and have been deposed once in December 2012 as an expert witness in a medical malpractice case. The case name was Sepe v. London.

OVERVIEW

Olmesartan Medoxomil, the active ingredient in the Benicar family of products (Benicar, Benicar HCT, Azor, Tribenzor, collectively referred to herein as "Benicar" and "olmesartan"), is indicated for the treatment of hypertension. Benicar is manufactured and sold by Daiichi Sankyo, and is within the class of anti-hypertensive medications known as Angiotensin II Receptor Blockers ("ARB's"). Benicar (the trade name) was first approved and marketed in the United States beginning in 2002, and then in Europe in 2003. Marthey, et al., Olmesartan-associated enteropathy: results of a national survey. Aliment Pharmacol Ther 2014; 40:1103-1109. There are many drugs on the market for the treatment of hypertension, including the other ARB's, angiotensin converting enzyme (ACE) inhibitors, and other medications and combinations of

medications are utilized as well. At all times starting with the initial marketing of Benicar there have been numerous safe and effective medications available for the treatment of hypertension, aside from Benicar.

The development process for Benicar is described in the deposition of Donald Hinman. Benicar's mechanism of action for the treatment of hypertenstion is linked to the small intestine, the location for activation of the pro-drug, olmesartan, with most absorption in the small intestine. (Donald Hinman, 81:8-22). The development history, structure, metabolism, and other technical background of olmesartan is summarized in a recent publication. Marietta, et al. Drug-Induced Enteropathy. Digestive Diseases 2015;33:215-220. Of note, the pre-clinical and clinical testing that was performed was not adequately powered or designed to study gastrointestinal adverse effects. No specific test or study was performed prior to marketing Benicar to determine whether there was any effect on the gastrointestinal system, and there was no clinical or preclinical study performed to determine whether olmesartan, "caused any changes to the villi in the intestine, the small intestine." (Donald Hinman, 29:14-22, 48:7-16). The lack of any study of potential gastrointestinal side effects prior to marketing Benicar is consistent with the fact that Benicar was not designed to have any impacts on the gastrointestinal system, and was not expected to cause sprue-like enteropathy, or a syndrome or constellation of symptoms that would present like celiac disease. (Allen Feldman, 69-70). The label for Benicar referenced diarrhea, seen in clinical studies, no greater than placebo, but this was not meant to describe a risk of chronic diarrhea. (Allen Feldman, 72). Of interest, Mr. Hinman testified that Daiichi Sankyo does not fully understand, "the entire process whereby the drug is absorbed, metabolized and acts within the

body...The full extent of the mechanism of action is not fully understood." (Donald Hinman, 128:8-130:5).

It is now firmly established in the medical literature that a subset of patients utilizing Benicar develop a gastrointestinal syndrome characterized as sprue-like enteropathy, with related gastrointestinal side effects as a result of using this medication. This condition is referenced internally by Daiichi Sankyo as olmesartan associated enteropathy, and olmesartan induced enteropathy, meaning that the enteropathy is caused by olmesartan. (Allen Feldman, 356:11-15) As set forth above, I refer to this condition as olmesartan enteropathy. This condition is characterized by delayed onset duration, generally with an onset in the range of months or (more often) years. The resulting clinical syndrome typically manifests with dehydration and other malabsorptive symptoms such as severe chronic diarrhea and/or vomiting, significant weight loss, abdominal pain, nausea, and related systemic effects. Where intestinal evaluation and biopsies are performed, the specimens generally demonstrate inflammatory changes including partial or total villous atrophy. Findings can include increased intraepithelial lymphocytes and microscopic colitis, among others. There is not a single invariable presentation for this condition, and the condition is ultimately diagnosed based on the clinical presentation and course, with particular attention to positive dechallenge or rechallenge. The findings on pathology can be useful in ruling out potential causes, and for correlation with the clinical presentation and course. Deposition testimony indicates that an internal Daiichi Sankyo document recognizes that where villous atrophy is identified this should be understood to be due to organic change in the small intestine, as opposed to a functional change such as with ordinary diarrhea. (Hideki Tagawa, 83:19-84:8). This condition has been misdiagnosed, most often as celiac disease in many patients, or other

inflammatory disorders due to the similar clinical presentations, and a lack of knowledge about olmesartan enteropathy in the medical community. Burbure, et al. Olmesartan-associated sprue-like enteropathy: a systematic review with emphasis on histopathology. Human Pathology (2016) 50, 127-134.

I first learned of an association between olmesartan and a sprue-like enteropathy in April 2012. My colleague Peter Green, founder and director of the Celiac Disease Center at Columbia University, mentioned a conversation he had with Joseph Murray, a celiac disease expert at the Mayo Clinic, about his findings that a number of patients thought to have refractory celiac disease or collagenous sprue had been taking olmesartan, and that their symptoms and histology resolved after discontinuation of the drug. At the time, this condition had not appeared in the medical literature, aside from a passing mention of olmesartan in Dr. Murray's 2010 publication on collagenous sprue. Rubio-Tapia, et al. Gluten-Free Diet and Steroid Treatment Are Effective Therapy for Most Patients with Collagenous Sprue. Clinical Gastroenterology and Hepatology 2010; 8:344-349. Upon hearing about this from Dr. Green, my colleagues and I reviewed the charts of our most treatment-resistant patients, and were struck by the fact that olmesartan was a common feature. I reached out to a number of patients at that time, informing them of this possible association, and advising them to discontinue the drug. This resulted in some of the most dramatic clinical improvements I have witnessed as a physician. To this day, some of my most grateful patients are those who went from being desperately ill, with weight loss and severe diarrhea necessitating multiple hospitalizations, to total clinical and histologic resolution after discontinuing olmesartan. Typically these are patients who have first been evaluated and treated (by me or others) with invasive procedures, and ineffective or transiently effective modalities

including a gluten-free diet, an elimination diet (involving extraordinary efforts to minimize cross-contamination by gluten), corticosteroids, and immunomodulators, prior to olmesartan being identified as the culprit.

By the time Dr. Murray's group published its series of 22 patients (Rubio-Tapia, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc. August 2012;87(8):732-738) in August 2012, my colleagues and I at the Celiac Disease Center at Columbia had a number of patients whom we diagnosed with this condition. By that time, I had started reintroducing dietary gluten to these patients and found that they remained healthy when doing so. We realized that patients with olmesartan enteropathy were being misdiagnosed as having celiac disease, given that these two conditions have similar histologic features. In addition, during this time, I was participating in a study evaluating our Center's experience of seronegative villous atrophy, the term used to describe the existence of duodenal villous atrophy with the absence of abnormally elevated celiac disease antibodies (tissue transglutaminase antibodies and deamidated gliadin peptide antibodies). Given the information we had received from Dr. Murray and our own experience of dechallenged patients who then improved, we reviewed the records that we had collected and found that, of 72 patients with seronegative villous atrophy, 16 (22%) were ultimately attributed to olmesartan use. Though we had not initially set out to study olmesartan in that paper, we found that olmesartan was the most common agent in those diagnosed with medication-related villous atrophy. DeGaetani, et al. Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma. Am J Gastroenterol 2013;108:647-653.

Despite the Mayo Clinic publication in 2012, the subsequent publication of our series corroborating Dr. Murray's experience, as well as additional case reports, and despite the label change on July 3, 2103, and the July 3, 2013 Safety Notification by the FDA stating that olmesartan can cause sprue-like enteropathy, I continued to see patients with severe malabsorption who, while taking olmesartan, were evaluated by one or more previous gastroenterologists and were told that they had refractory celiac disease. As a result of my knowledge of this condition, I adopted a practice where, when a referring colleague calls me, asking me to see a sick and complicated outpatient on short notice as a second opinion, I will first ask them if the patient is taking olmesartan, which has occasionally led to a rapid diagnosis and resolution of the problem while under the care of the referring physician, without the patient even coming to our center for formal evaluation. The now established fact that olmesartan is a cause of villous atrophy and sprue-like enteropathy is not a matter of dispute in the medical community. For example, in addition to the FDA safety notification, and many references in the literature, olmesartan is now listed as a *cause* of villous atrophy in the widely-used physician reference Up To Date:

Causes of small intestinal villous atrophy other than celiac disease

Small intestinal bacterial overgrowth
Crohn disease
Cow's milk or soy protein intolerance (children)
Eosinophilic gastroenteritis
Giardiasis
Intestinal lymphoma
Peptic duodenitis
Post-gastroenteritis
Tropical sprue
Zollinger-Ellison syndrome
Common variable immunodeficiency
Autoimmune enteropathy
Other immunodeficiency states (usually apparent clinically, eg, AIDS enteropathy, hypogammaglobulinemic sprue)
Medications (eg, olmesartan)
Whipple disease
Malnutrition
Intestinal tuberculosis
Graft-versus-host disease

Based on my knowledge, education, training, and experience, which includes the diagnosis and treatment of numerous patients with olmesartan enteropathy, my knowledge of the medical literature, and my review and analysis of the documents and information referenced in this report, it is my opinion to a reasonable degree of medical certainty that Olmesartan causes sprue-like enteropathy and related side effects in a subset of patients utilizing the drug, which I refer to as olmesartan enteropathy herein.

I. The Medical Literature

The first mention of the condition that came to be known as olmesartan enteropathy was made in a 2010 case series of collagenous sprue reported by Joseph Murray's group at the Mayo Clinic. Rubio-Tapia, et al. Gluten-Free Diet and Steroid Treatment Are Effective Therapy for

Most Patients with Collagenous Sprue. Clinical Gastroenterology and Hepatology 2010; 8:344-349 This retrospective review consisted of patients with collagenous sprue seen at three Mayo sites (Rochester, Jacksonville and Scottsdale) during the years spanning 1993-2009. Collagenous sprue is a form of enteropathy that is characterized by villous atrophy (characteristic of celiac disease as well) and additionally a thickened band of subepithelial collagen. A total of 30 patients were identified, the great majority of whom (97%) had weight loss, and all of whom had diarrhea. A concomitant diagnosis of celiac disease was noted in 11 (37%) of these patients, though only 6 of these 11 patients had a history of elevated celiac disease serologies. The authors noted that 8 of the 30 patients (27%) had been taking olmesartan; this is especially impressive given that more than half of the time span of this study occurred prior to the approval and availability of olmesartan. The main focus of the paper is on outcomes and response to the gluten-free diet and immunosuppressive therapy, but the authors note the following in the Discussion, when making the point that antifibrotic therapy may not necessarily be effective for this condition: "Indeed, olmesartan, a drug with antifibrotic properties outside the gastrointestinal tract, was used by one third of our patients."

In 2012, Dr. Murray's group published a case series of olmesartan enteropathy consisting of 22 patients, 2 of whom were previously included in their report on collagenous sprue. Rubio-Tapia, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc. August 2012;87(8):732-738 All 22 patients had chronic diarrhea, duodenal biopsies showing villous atrophy, alternative causes ruled out, and a clinical improvement after discontinuation of olmesartan. The majority (16/22, 73%) were previously diagnosed with either non-responsive/refractory celiac disease or unclassified sprue. The mean duration of olmesartan use

prior to the development of symptoms was 3.1 years. Weight loss was a prominent symptom, and ≥10 kg of weight loss was reported in 19 of the 22 patients (86%). After olmesartan withdrawal and clinical improvement, a follow-up duodenal biopsy was performed in 18 patients, 17 of whom (94%) had histologic recovery of villous atrophy (while the 18th patient had marked improvement from total villous atrophy to focal partial villous atrophy). All patients improved upon dechallenge, and deliberate rechallenge was not performed due to the severity of the risk; however, the authors note that a rechallenge occurred in the history of 4 patients:

> No deliberate rechallenge test with olmesartan was undertaken because of the life-threatening nature of the syndrome, although 2 patients reported anecdotally that their symptoms had worsened when they restarted olmesartan before the potential association was recognized, and 2 patients experienced improvement when olmesartan was stopped when they were hospitalized (for dehydration and hypotension) and worsened in the weeks following discharge and re- introduction of olmesartan.

Of note, though Dr. Murray's study of patients with olmesartan enteropathy was not discussed in the literature prior to 2012, Daiichi Sankyo was aware of the fact that Dr. Murray was seeing patients with sprue-like symptoms while taking olmesartan medoxomil. Dr. Murray contacted Daiichi Sankyo to inquire of the company as to any information that could be shared regarding "data pertaining to colitis, enteritis, or sprue-like symptoms," in 2009, about "possible side effects of olmesartan, specifically Benicar and the association with unsual and rare enteropathy malapsorption," in 2010, and reporting, "five patients experienced enteropathy like disease while taking olmesartan," in 2011. (Allen Feldman, 370-389, Exhibits 359, 360, 361). As discussed below, by 2009 when Dr. Murray contacted the company (and earlier) Daiichi Sankyo already had received numerous compelling adverse event reports regarding patients with the

clinical syndrome presented with olmesartan enteropathy (i.e. chronic diarrhea, dehydration, severe weight loss, reports of positive dechallenges and rechallenges, hospitalizations).

Following the case series by Dr. Murray's group, additional sporadic case reports were published from institutions in Pennsylvania, Ohio, and Texas. The reference list to this report lists numerous additional case reports. Dreifuss SE1, Tomizawa Y, Farber NJ, Davison JM, Sohnen AE. Spruelike enteropathy associated with olmesartan: an unusual case of severe diarrhea. Case Rep Gastrointest Med. 2013;2013:618071; Stanich PP1, Yearsley M, Meyer MM. Olmesartan-associated sprue-like enteropathy. J Clin Gastroenterol. 2013 Nov-Dec;47(10):894-5; Nielsen JA1, Steephen A, Lewin M. *Angiotensin-II inhibitor (olmesartan)-induced collagenous sprue with resolution following discontinuation of drug.* World J Gastroenterol. 2013 Oct 28;19(40):6928-30. . In addition to these individual case reports, three additional case series were published on this condition in 2013-2014. I co-authored a case series of patients at the Celiac Disease Center at Columbia University on the topic of seronegative villous atrophy, in which we found that 16 of 72 patients with this condition (22%) had olmesartan enteropathy. Olmesartan was the most common cause of drug-induced villous atrophy in our series (16 of 19 patients, 84%). DeGaetani, et al. Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma. Am J Gastroenterol 2013;108:647-653 A case series from a single institution in France described 5 patients with diarrhea attributed to olmesartan, of whom 3 had villous atrophy on duodenal biopsy. Theophile, et al. Five cases of sprue-like enteropathy in patients treated by olmesartan. Dig Liver Dis. 2014 May;46(5):465-9 Another series of 3 patients with villous atrophy attributed to olmesartan was reported by investigators in Rome. Ianiro G1, Bibbò S, Montalto M, Ricci R, Gasbarrini A, Cammarota G. Systematic review: Sprue-like

enteropathy associated with olmesartan. Aliment Pharmacol Ther. 2014 Jul;40(1):16-23. By that time, the accumulating case reports and series were growing at a pace that prompted those writers to include a review of the literature; they found that 54 patients were reported as diagnosed with olmesartan enteropathy to date. See Ianiro, et al.

The first publication to discuss the gastrointestinal effects of olmesartan using a control group was a letter published by two investigators for the ROADMAP study of olmesartan, which was designed to study a primary endpoint of occurrence of microalbuminuria, in reply to Dr. Murray's case series. Menne, Haller. Olmesartan and Intestinal Adverse Effects in the ROADMAP Study. Mayo Clin Proc. December 2012;87(12):1230-1232. This letter reported that, among patients participating in a randomized trial of olmesartan use in diabetics, the development of treatment emergent adverse events was not significantly different among those randomized to olmesartan (3.5%) compared to those randomized to placebo (4.2%, p=0.20). Diarrhea was specifically queried, and this symptom was present in the same proportion of those receiving drug and placebo (2.3%). Although the authors argued that "our observation in a large group of diabetic patients treated with 40 mg of olmesartan daily does not support this conclusion" that olmesartan is directly involved in sprue-like enteropathy, these findings do not rule out causality for an uncommon adverse event that occurs with long-term use of the drug. This analysis consisted of 2,232 patients exposed to olmesartan for a median of 3.2 years. Given that the mean onset to symptoms in Murray's case series was 3.1 years, and given the unknown incidence of olmesartan enteropathy, this subanalysis of a clinical trial is insufficient to assess for causality. Indeed, the purpose of phase 4 evaluation is to test long-term, less common adverse events induced by the drug; a phase 3 study would not be adequately powered to pick up a signal

in the case of a rare event. Moreover, the article published in the New England Journal of Medicine with regard to the study does not discuss gastrointestinal side effects. Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope LM, Rump LC, Viberti G; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011 Mar 10;364(10):907-17; (Jeffrey Warmke, 192:14-19). The case report forms also do not specify gastrointestinal side effects as an adverse event to be watched, and the investigators were not told about the adverse event reports the company was accumulating for patients with severe gastrointestinal side effects. (Jeffrey Warmke, 109:16-110:3, 110:4-11, 110:12-18, 111:19-112:7, 113:3-20, 145:21-146:11, 157:15-158:5). These factors, combined with the delayed onset of the condition, could have resulted in cases of olmesartan enteropathy being missed. Daiichi Sankyo employee Jeffrey Warmke testified in his deposition that the ROADMAP study was not designed to study gastrointestinal side effects, and was not adequately powered to study gastrointestinal side effects or any of the secondary endpoints of the study, and the study population was different from the general population taking Benicar in the United States. (Jeffrey Warmke, 88:8-15, 111:5-11, 272:19-274:11, 362:12-363:23). Notwithstanding, Dr. Warmke did acknowledge that there were patients who presented with clinical symptoms of olmesartan enteropathy, including dechallenge and rechallenge, and assessment by Daiichi Sankyo as probably related to the drug. This includes one patient who had a documented dechallenge and rechallenge in December, 2006 and January, 2007, and Dr. Warmke acknowledged that Daiichi Sankyo had first hand information that olmesartan likely caused these symptoms. One patient had documented villous atrophy, and another had documented collagenous colitis found by the investigator to be

definitely caused by the drug. (Exhibits 3047, 3048, 3049, 3051; Jeffrey Warmke, 327:21-334:24, 337:2-339:17, 340:14-346:21, 347:15-350:10). The letter to the Mayo Clinic Journal, authored by the lead investigators of the study, does not discuss these specific patients since it was limited to an aggregate analysis of trial participants, and acknowledges that a signal could have been missed due to the limited size and duration of the study. In sum, the ROADMAP study does not disprove association or causality for olmesartan enteropathy, and in fact study patients have been identified who likely developed the condition.

I was the senior investigator of two studies evaluating olmesartan enteropathy that included a control population. In both of these studies, we studied the question of whether the cases of olmesartan enteropathy in the literature represent a "tip of the iceberg" phenomenon. The first study was a case-control study consisting of patients at Columbia University Medical Center who were undergoing upper endoscopy or colonoscopy. Greywoode, et al. Olmesartan, Other Antihypertensives, and Chronic Diarrhea Among Patients Undergoing Endoscopic Procedures: A Case-Control Study. Mayo Clin Proc. September 2014;89(9):1239-1243. We sought to determine whether olmesartan use was more common among patients noting diarrhea as the reason for their procedure as compared to controls who underwent their procedure for another reason. We found that there was no statistically significant association between olmesartan use and diarrhea in this population. However, as we acknowledged in the Discussion section of that paper, "there was also a relatively small prevalence of use of olmesartan (0.7%-1%) among study patients, limiting the power of this analysis. Because the upper bound of our 95% CI was 5.00 in the EGD analysis and 1.74 in the colonoscopy analysis, a meaningful

association between olmesartan and diarrhea may exist that was not detectable because of the relative rarity of use of olmesartan."

Recognizing that the low number of users of olmesartan in our medical center limited our power to detect a signal when using olmesartan exposure as an outcome in a case-control setting, our second study investigating a potential "tip of the iceberg" sampled patients based on exposure to olmesartan. Lagana, et al. Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers. J Clin Pathol 2014;0:1-4. In a cross-sectional study, we compared 20 olmesartan users who underwent duodenal biopsy for evaluation of abdominal pain and compared them to a population of age and sex-matched non-olmesartan controls who also underwent duodenal biopsy for abdominal pain. The outcome of interest was the presence of one or more of the following histologic features: villous atrophy, crypt hyperplasia, mean maximum intraepithelial lymphocyte count, generalized intraepithelial lymphocyte increase, chronic inflammation, eosinophilia, neutrophilia, or increased crypt apoptosis. We found that, although ≥ 1 of these features was present in 50% of the olmesartan group and this was greater than that of controls (20%), this did not meet statistical significance ($p=0.10$). From a statistical standpoint, the study was likely underpowered to detect a signal of subtle histologic abnormalities related to olmesartan. We therefore concluded that: "This study raises the possibility that there may be a spectrum of injury associated with olmesartan use, apart from the severe syndrome that causes life-threatening diarrhea." Of note, we discussed a case report we defined as having "considerable relevance to our study," describing a patient who presented with constipation, but not diarrhea, and varied findings on duodenal biopsy. Talbot GH. Small bowel histopathologic findings suggestive of celiac disease in an asymptomatic

patient receiving olmesartan. Mayo Clin Proc. 2012;87:1231-2 Based on my continued study of olmesartan enteropathy, including reports of patients with variable presentations and clinical symptoms, it is likely that there is a spectrum of injury.

We conducted these two studies so as to better characterize the clinical spectrum of olmesartan enteropathy. The null findings of the case-control study and cross-sectional study suggest that olmesartan is not a common cause of diarrhea among patients undergoing endoscopy, and that olmesartan does not cause far greater histologic abnormalities in individuals who have abdominal pain as compared to those who do not take olmesartan. However, this does not detract from the overall question of causality. These investigations should be seen in the context of studying and defining the boundaries of the condition. The case that the relationship between olmesartan and enteropathy is causal is well established based on the numerous dechallenge studies decribed in the case series and reports above. In general, when adverse effects are events that occur commonly in the general population (such as diabetes or depression), it may be difficult to be certain that the event occurred due to the agent, and abatement of the event after withdrawal of the agent may be suggestive, but not definitive for causality. In contrast, the clinical presentation of olmesartan enteropathy is not commonly seen. For example, one of the findings often seen with this condition, intestinal villous atrophy, has a limited number of causes and does not occur commonly in the general population. Where alternative causes of villous atrophy can be ruled out (e.g. negative celiac serologies, and a lack of a response to a gluten-free diet in the case of celiac disease, and a resolution of villous atrophy after discontinuation of olmesartan despite resumption of a gluten-containing diet), the establishment of causality is straightforward.

In addition to the fact that dechallenge and rechallenge strongly establishes causality, our understanding of this relationship was strengthened by a nationwide cohort study by Basson and colleagues that provided helpful data on the temporality as well as the strength of the relationship. Basson, et al. Severe malabsorption associated with olmesartan: a French nationwide cohort study. Gastroenterology 2014; 146:S-114. In that study, which evaluated more than 4 million adults in France prescribed an ACE inhibitor or an angiotensin receptor blocker (ARB, including olmesartan), the authors found that, compared to users of ACE inhibitors, users of olmesartan had a more than two-fold increased risk of hospitalization for malabsorption overall (adjusted rate ratio [ARR] 2.49; 95%CI 1.73-3.57). Moreover, when stratified by duration of time on the drug, this association was not found among those with <1 year of exposure (ARR 0.76; 95%CI 0.39-1.49) but was markedly increased among those with >2 years of exposure (ARR 10.65; 95%CI 5.05-22.46). This finding, of a large effect size when evaluating long-term use, supports the conclusion that the risk of this outcome is related to the duration of drug use, lending credence to both the strength of association and a biological gradient. The absolute rate of hospitalization for malabsorption occurred in 48 patients over the course of 860,894 person-years. This yields a rate of 5.6 events per 100,000 person-years of observation. Though this is likely an underestimate of the rate of olmesartan enteropathy (given that outpatients with the condition were not counted), the order of magnitude of this rate provides a strong explanation as to why diarrhea was not detected in users of olmesartan in the ROADMAP study; the latter study had an insufficient number of patients followed for an insufficient period of time to detect this adverse event.

It is also notable that the authors found a strong effect size when evaluating olmesartan use for >2 years and a subsequent hospitalization with a discharge diagnosis of celiac disease (ARR 10.21; 95%CI 4.21-24.76). Given the histologic resemblance of olmesartan enteropathy with celiac disease, these patients were likely misdiagnosed with celiac disease, analogous to the numerous patients described as having been diagnosed with celiac disease in adverse event reports to Daiichi Sankyo, and the many misdiagnoses documented in the literature (for example, the patients discussed in the August 2012 Rubio-Tapia article who were initially diagnosed with celiac disease).

The delayed onset of olmesartan enteropathy is described across the literature. This is likely due to the as-yet fully characterized nature of the immune response to this medication. Unlike a classical drug allergy that is typically apparent within 24 hours of initial exposure and is mediated by mast cell activation and/or circulating immunoglobulin E, olmesartan enteropathy typically develops after a prolonged period of drug exposure, congruent with the mean exposure of 3.1 years reported by Murray's group. There are two broad ways to think about how a drug can cause an outcome over long time horizon: accumulated toxicity and a co-factor. An example of accumulated toxicity is the undisputed causal link between cigarette smoking and lung cancer. This adverse effect of cigarette smoking is delayed because the cellular damage and accompanying inflammation that occurs with smoking is cumulative, and multiple resultant genetic mutations need to occur before this results in cancer. Hence the risk of lung cancer rises decades after an individual begins smoking because of the time required to accumulate cellular damage. The second prototype of delayed drug toxicity is that requiring a co-factor. For example, Reye's Syndrome, a rapidly progressive illness characterized by encephalopathy and

liver failure, was linked to aspirin use by children, but this condition only develops in the context of an acute viral illness, a co-factor that is necessary for the development of this drug-mediated illness. The present evidence points to this latter mechanism of a co-factor that triggers olmesartan enteropathy. Just as individuals at any age can develop celiac disease, in which gluten induces villous atrophy after years of gluten exposure without ill effect, olmesartan (like gluten in celiac disease) likely requires an as-yet unidentified co-factor upon which exposure to this drug induces villous atrophy. (It should be noted that the co-factor that triggers celiac disease in individuals after years of gluten exposure has not been identified, but this does not at all undercut the indisputable causal link between gluten and villous atrophy among patients with celiac disease.)

The mechanistic study by Dr. Murray's group points to a biologically plausible mechanism by which olmesartan induces enteropathy after a variable period of exposure. Marietta EV, Nadeau AM, Cartee AK, Singh I, Rishi A, Choung RS, Wu TT, Rubio-Tapia A and Murray JA. Immunopathogenesis of olmesartan-associated enteropathy. Aliment Pharmacol Ther. 2015 Dec;42(11):1303-14. This study consisted of immunohistochemical analysis of patients with known olmesartan enteropathy (including patients both on and off olmesartan) as well as immunofluorescent analysis of generic human intestinal epithelial cells (Caco2 cells) after in vitro incubation with olmesartan for 4 hours. The authors found that incubation of these cells with olmesartan resulted in the expression of IL-15, a cytokine that has been broadly implicated in refractory celiac disease. Malamut G, et al. *IL-15 triggers an antiapoptotic pathway in human intraepithelial lymphocytes that is a potential new target in celiac disease-associated inflammation and lymphomagenesis.* J Clin Invest. 2010 Jun;120(6):2131-43. When

incubating these cells with losartan and telmisartan, this finding was not observed. This *in vitro* demonstration of a pro-inflammatory cytokine release (particularly one that is closely associated with refractory celiac disease, a histologic mimicker of this condition), one that is specific to olmesartan among members to this drug class, adds biologic plausibility to the case for causality. Stated another way, this study likely establishes the biological mechanism whereby olmesartan causes this clinical syndrome. As recognized by Daiichi Sankyo, olmesartan clearly causes biological changes to the small intestine, leading to some or all of the findings and symptoms of olmesartan enteropathy, including inflammation, villous atrophy, malabsorption, chronic diarrhea and/or vomiting, dehydration, abdominal pain, nausea, and severe weight loss, and in some patients systemic effects due to the resulting lack of absorbed nutrients.

A. Variation In Clinical Presentation of Olmesartan Enteropathy

It is important to discuss the variable presentation of olmesartan enteropathy, in terms of the clinical presentation and severity of symptoms. There is literature supporting a spectrum of severity, with varied clinical pictures, likely due to the stage of development of the syndrome. For example, the French nationwide cohort study by Basson, et al [Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. Gut. 2016 Oct;65(10):1664-9] was restricted by definition to those who whose clinical condition was sufficiently severe so as to warrant hospitalization, while in the case series by Rubio-Tapia, et al [Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT and Murray, JA. Severe Spruelike Enteropathy Associated With Olmesartan. Mayo Clin Proc. 2012 Aug;87(8):732-8. Epub 2012 Jun 22.] 36% of patients did not require hospitalization. It is also

possible that patients with mild or minimal symptoms but with laboratory abnormalities could have an attenuated form of this condition. This was suggested by Talbot, et al who described a patient who was taking olmesartan and had anemia and reflux; though he did not have diarrhea, he was found to have mild villous blunting and increased intraepithelial lymphocytosis, akin to a mild form of celiac disease.Talbot GH. Small bowel histopathologic findings suggestive of celiac disease in an asymptomatic patient receiving olmesartan. Mayo Clin Proc. 2012 Dec;87(12):1231-2. Though there is less certainty regarding the scope of a mild form of olmesartan enteropathy, given the wide spectrum of clinical severity documented in celiac disease, together with the fact that the majority of patients with celiac disease are undiagnosed, it is reasonable to conclude that there is a clinical and histologic spectrum of severity for olmesartan enteropathy, wherein the more mild cases go undetected and untreated. Rubio-Tapia A1, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012 Oct;107(10):1538-44; quiz 1537, 1545. doi: 10.1038/ajg.2012.219. Epub 2012 Jul 31.

This opinion is further supported by additional reports in the literature. One article addressing two cases reports of olmesartan enteropathy discusses the potential for a "patchy" presentation in the duodenum, and, "that olmesartan-associated enteropathy is a new entity with a wide spectrum of histological small bowel abnormalities." Schiepatti, et al. **Olmesartan-associated enteropathy: new insights on the natural history? Report of two cases.** Scandinavian Journal of Gastroenterology. 2015; Early Online: 1-5. Another article, cited in Schiepatti, et al., states: "We report four patients with olmesartan-associated enteropathy and normal villi. The clinical picture was that of severe diarrhoea, similar with that of patients with

villous atrophy, and these four patients also improved after olmesartan withdrawal. These cases add to the description of olmesartan-associated enteropathy. It may include patients with a wide range of histological duodenal abnormalities, from isolated intra-epithelial lymphocytosis and lamina propria lymphocytic infiltration to total villous atrophy. In addition, there is evidence of involvement of almost the entire gut in this condition." In terms of causation, the authors state: "This study supports the causality of the association between olmesartan and enteropathy. Firstly, our cases and those reported by Rubio Tapia et al. were remarkably similar. Secondly, nondeliberate interruptions followed by reintroductions led to clinical remissions followed by clinical relapses repectively. Thirdly, as in the study by Rubio Tapia et al., duodenal mucosa returned to normal after olmesartan withdrawal." Marthey, et al. **Olmesartan-associated enteropathy: results of a national survey.** Aliment Pharmacol Ther 2014; 40: 1103-1109.

Another case report discusses a patient with olmesartan enteropathy who suffered a colon perforation, in a patient reporting, "recurrent mild abdominal pain, bloating, nausea, occasional vomiting, and severe nonbloody diarrhea with 20 evacuations a day for one year. She had a 45 pound weight loss with six months…Celiac disease was excluded by negative conventional serology tests…and the absence of a clinical response to a gluten-free diet…Olmesartan associated enteropathy was suspected and the drug was discontinued and replaced by lisinopril. One month later, she had complete resolution of the abdominal discomfort and diarrhea. After 5 months the patient continued to be asymptomatic with no gastrointestinal manifestations." Abdelghany, et al. **Olmesartan Associated Sprue-Like Enteropathy and Colon Perforation.** Case Reports in Gastrointestinal Medicine. Volume 2014, Article ID 494098, 2014.

B. Resulting Systemic Harm From Olmesartan Enteropathy

Malabsorption has clinical consequences that go beyond the acute presentation of dehydration, diarrhea, vomiting, and weight loss. Celiac disease is known to cause a wide range of such systemic consequences, and the similar manifestation of olmesartan enteropathy exposes the patient to a similar spectrum of harms.. The list of systemic harms resulting from olmesartan enteropathy may include, in no particular order of importance or frequency, steatorrhea, fatigue or weakness, neuropathy, hair loss, muscle wasting, renal compromise and damage, anemia, and others. These symptoms can have a significant detrimental impact on a patient's quality of life. Based on our knowledge of the impact of celiac disease on morbidity, we can infer that there is analogous burden among those with olmesartan enteropathy. For instance, anemia is a common consequence of malabsorption, as has been observed both in celiac disease [Abu Daya H1, Lebwohl B, Lewis SK, Green PH. Celiac disease patients presenting with anemia have more severe disease than those presenting with diarrhea. Clin Gastroenterol Hepatol. 2013 Nov;11(11):1472-7.] and olmesartan enteropathy (present in 45% of patients in one systematic review).[Ianiro G1, Bibbò S, Montalto M, Ricci R, Gasbarrini A, Cammarota G. Systematic review: Sprue-like enteropathy associated with olmesartan. Aliment Pharmacol Ther. 2014 Jul;40(1):16-23..] This can result in significant fatigue and can take months to reverse. Moreover, many patients with olmesartan enteropathy were treated with corticosteroids in addition to a gluten-free diet; this was the case in 20 of the 22 patients (91%) in Rubio-Tapia's initial case series.[Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT

and Murray, JA. Severe Spruelike Enteropathy Associated With Olmesartan. Mayo Clin Proc. 2012 Aug;87(8):732-8] Corticosteroid treatment can have numerous adverse consequences, both short-term (including hyperglycemia, neuropsychiatric symptoms, and swelling in the extremities and face) and long-term (cataracts and worsened bone density, increasing the risk of fracture). Since many patients with olmesartan enteropathy have been and likely continue to be treated with a gluten-free diet under the erroneous impression of a celiac disease diagnosis, the burden of this diet should be considered. This diet is expensive, socially isolating, and can impair quality of life; patients with celiac disease who are maintaining this diet have rated its burden as considerable.

Shah S, Akbari M, Vanga R, Kelly CP, Hansen J, Theethira T, Tariq S, Dennis M, Leffler DA. Patient perception of treatment burden is high in celiac disease compared with other common conditions. Am J Gastroenterol. 2014 Sep;109(9):1304-11.

II. Methodology

The clinical process to identify olmesartan enteropathy as the likely cause of a patient's symptoms is one of differential diagnosis. In our publication on seronegative villous atrophy, DeGaetani, et al., we discuss the following diagnostic algorithm:

> We propose that all patients with seronegative VA should initially be tested for HLA DQ2 and DQ8. If the test is negative, we would usually exclude CD. Immunoglobulin deficiency should also be excluded, both selective IgA deficiency and CVID. A thorough history should be obtained, which should include medication and travel history.

In clinical practice, this translates into the assessment for use of olmesartan (and other medications) during the initial history taking. Among patients with villous atrophy who report

taking olmesartan, at our institution we have deemed the causality to be so strong in this group of patients that we advise discontinuing olmesartan and switching to an alternative anti-hypertensive agent in consultation with the prescriber of that medication (e.g. the patient's internist or cardiologist who is treating the patient's hypertension). In my experience patients with seronegative villous atrophy who were taking olmesartan at the time of assessment had resolution or marked improvement of symptoms and villous atrophy upon discontinuation of the drug. An illustrative Case Report regarding a patient hospitalized three times for severe dehydration and acute renal failure, later found to have olmesartan enteropathy, describes this approach: "Olmesartan-induced enteropathy should be in the differential diagnosis for patients who present with severe unexplained chronic diarrhea and weight loss. Moreover, in patients with a working diagnosis of CD but negative CD-specific serology or lack of response to a gluten-free diet, a review of current medications is desirable before resorting to other expensive investigations." Rishi, A., Garland, K. Unusual Severe Side Effect of a Commonly Used Drug. Journal of Clinical Hypertension, 2015.

There is a spectrum of potential causes for the combination of symptoms that is seen with olmesartan enteropathy. In the evaluation of causation for a particular patient, the generally applicable components of the differential diagnosis will usually include celiac disease (discussed above), as well as irritable bowel syndrome (ulcerative colitis, Crohn's disease), autoimmune enteropathy, and medication induced enteropathy. The appropriate differential for a particular patient is established through application of this general process, informed by a thorough history and physical exam, with particular attention to co-morbidities, time of onset, nature of the symptoms, medications, and other medically significant facts. Other potential causes may merit

consideration based on this process. One must then evaluate the clinical course, particularly dechallenges and rechallenges, in ruling out/in aspects of the differential diagnosis.

Of particular importance are documented dechallenges, and even more so, rechallenges. This information is important not just from a clinical perspective, but also from an epidemiological perspective. When determining whether a drug is associated with an adverse outcome, the strength of association depends on certain aspects of each case, including temporality (i.e. that the adverse event did not pre-date the exposure to the drug) and abatement of the adverse effect after withdrawal of the drug (i.e. dechallenge). The recurrence of the adverse effect after the resumption of the medication provides particularly strong evidence that an adverse drug effect is occurring. Though case reports are generally low on the hierarchy of evidence when assessing for causality, evidence from a rechallenge is particularly strong. To cite a textbook of pharmacoepidemiology, Strom B, Kimmel S, Hennessey S. Textbook of Pharmacoepidemiology 2nd edition p23.:

> Case reports can be particularly useful to document causation when the treatment causes a change in disease course which is reversible, such that the patient returns to his or her untreated state when the exposure is withdrawn, can be treated again, and when the change returns upon repeat treatment.

Scoring systems, such as the Naranjo algorithm, a widely used method for grading suspicion of causality, place special emphasis on rechallenge.[García-Cortés M1, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ; Spanish Group for the Study of Drug-induced Liver Disease (grupo de Estudio para las Hepatopatías Asociadas a Medicamentos, Geham). Evaluation of Naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. Aliment Pharmacol Ther. 2008 May;27(9):780-9.] In the Naranjo algorithm, the greatest

number of points (+2) are assigned to the following two parameters: 1) occurrence of the event after exposure to the drug; and 2) in individual cases a positive rechallenge. As noted above, the original case series by Rubio-Tapia noted that a deliberate rechallenge was not performed but that 4 of the 22 patients had experienced a recurrence of symptoms upon reintroduction of the medication, a *de facto* rechallenge.[Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT and Murray, JA. Severe Spruelike Enteropathy Associated With Olmesartan. Mayo Clin Proc. 2012 Aug;87(8):732-8] Rechallenge evidence was also noted in the Medwatch report cited above (Medwatch report number SU-2007-005968).

The evidence to be presented below will consider the Bradford Hill criteria for causality. Strom, et al. These criteria consist of biological plausibility (see above under Medical Literature),[Marietta EV, Nadeau AM, Cartee AK, Singh I, Rishi A, Choung RS, Wu TT, Rubio-Tapia A and Murray JA. Immunopathogenesis of olmesartan-associated enteropathy. Aliment Pharmacol Ther. 2015 Dec;42(11):1303-14.] the strength of the association (see rate ratios reported below by Basson, et al [Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. Gut. 2016 Oct;65(10):1664-9.], the consistency of symptomatology (see adverse event reports and case series below), specificity (the paucity of sprue-like enteropathy reported in other antihypertensives and the quantititative difference when comparing olmesartan use to angiotensin converting enzyme inhibitors),[Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. Severe intestinal malabsorption

associated with olmesartan: a French nationwide observational cohort study. Gut. 2016 Oct;65(10):1664-9.] and temporality (see adverse event reports and case series below).

The term "associated" rather than "induced" was initially used by Dr. Murray, likely due to his exercising caution when describing a new entity, mindful of the ever-present scientific practice to avoid confusing correlation with causation. The magnitude of the clinical improvement upon dechallenge in his and our case series and the absence of suspicious confounding variables in the cases described left little doubt that olmesartan was causing this syndrome, but the condition continued to be described as "associated with olmesartan" as reports accrued in the literature, in following the convention of naming this newly-defined condition. In fact, there are statements recognizing causality in more recent publications on which Dr. Murray is a co-author. One states: "All of these reports clearly demonstrate that administration of olmesartan to some individuals can lead to severe enteropathy." Marietta, et al. Drug-Induced Enteropathy. Digestive Diseases 2015;33:215-220. In another, "Olmesartan appears to cause a spruelike enteropathy, but it has not been shown to trigger celiac disease per se," and then at the end recognizes that olmesartan, "induces VA." Marild, et al. Blockers of Angiotensin Other Than Olmesartan in Patients With Villous Atrophy: A Nationwide Case-Control Study. Mayo Clin Proc. 2015;90(6):730-737. In an invited editorial authored with J.F. Ludvigsson, one of my co-authors in the Marild, et al. article, we stated in part: "when one considers a more specialised population, such as those referred to a coeliac disease centre for seronegative villous atrophy or those with collagenous sprue, olmesartan appears to be a prominent, even common, cause of these uncommon conditions." Lebwohl, B., Ludvigsson, J.F. Editorial: sprue-like enteropathy due to

olmesartan and other angiotensin receptor blockers – the plot thickens. Aliment Pharmacol Ther 2014; 40:1241-1249. In addition, the FDA states: "The U.S. Food and Drug Administration (FDA) is warning that the blood pressure drug olmesartan medoxomil (marketed as Benicar, Benicar HCT, Azor, Tribenzor, and generics) can cause intestinal problems known as sprue-like enteropathy." FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil. July 3, 2013 (Note: This report does not address any opinions regarding the adequacy of the warning added to the label). I was also co-author of an article recognizing causality prior to the FDA Safety Communication was issued, indicating, "before identifying olmesartan as a cause of VA, we too had considered 30% of our seronegative patients to have [unclassified sprue]." DeGaetani, et al. Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma. Am J Gastroenterol 2013;108:647-653. While caution when attributing causality is a prudent scientific habit at the outset as data is generated, in the case of olmesartan enteropathy, sufficient evidence has accumulated so as to conclude that this drug causes enteropathy in a subset of patients.

III. Adverse Event Reports

I have reviewed a number of adverse event reports produced from the files of Daiichi Sankyo, documenting patients exhibiting symptoms of olmesartan enteropathy. The adverse event reports present numerous cases supporting the finding of causation, dating back to 2003. Perhaps most significant is the repeated presentation of this clinical syndrome, inclusive of dechallenges successfully improving or alleviating the symptoms, and rechallenges resulting in